RESULTS OF A STUDY TO CORRELATE SERUM PROSTATE SPECIFIC ANTIGEN AND REPRODUCTIVE HORMONE LEVELS IN PATIENTS WITH LOCALIZED PROSTATE CANCER

Srinivasan Vijayakumar, MD, Syed Farhat Quadri, PhD, Liming Dong, MS, Lani Ignacio, RN, Indrajeet N.S. Kathuria, MBA, Harold Sutton, MD, and Howard Halpern, MD
Chicago, Illinois

This cross-sectional study was undertaken to determine whether serum hormones (free testosterone, androstenedione, luteinizing hormone, or prolactin) have any influence on serum prostate specific antigen (PSA) levels in patients with stage A-C prostate cancer. Blood samples were collected prior to any treatment in 36 patients; in 19 (group 1), three blood samples were collected 10 minutes apart between 9:00 AM and 9:30 AM for each patient and pooled together to avoid diurnal and episodic variation in serum testosterone values. In the remaining patients, only one sample could be collected (group 2). Free testosterone, androstenedione, luteinizing hormone, prolactin, and PSA levels were determined with appropriate radioimmunoassay techniques. Statistical analyses were performed separately for groups 1 and 2, and then with pooled data.

None of the hormones in any of the analyses showed any association to serum PSA values except for prolactin for the pooled data and for group 2. This statistical significance for prolactin disappeared on multivariate analysis. There were 21 African-American men and 15 whites in the study; no racial differences in hormonal levels were found except for lower luteinizing hormone levels in African Americans in group 2 and pooled data. No differences were found between group 1 and group 2 in the mean serum prolactin and luteinizing hormone values.

Serum free testosterone, androstenedione, and luteinizing hormone appeared to have no influence on serum PSA values in nonmetastatic cancer patients. Serum prolactin values were inversely associated with PSA values in univariate analysis for the pooled data; this disappeared in multivariate analysis. Unlike other studies that found higher serum testosterone levels in African-American college students than whites, no such differences were seen in this age group. Luteinizing hormone was lower in African-American men than in whites in the pooled study population. Further studies are needed to clarify our findings. (*J Natl Med Assoc.* 1995;87:813-819.)

Key words • prostate cancer • prostate specific antigen • serum reproductive hormones

Prostate specific antigen (PSA) is a sensitive and useful tumor marker in screening, staging, and follow-up of prostate cancer patients.[1] Serum PSA levels are influenced by the age of the patient, the stage and grade of the tumor, procedures such as digital rectal examination and

From the Departments of Radiation Oncology and Nuclear Medicine, Michael Reese Hospital, the Center for Radiation Therapy, and the Department of Statistics, University of Chicago, Chicago, Illinois. Presented at the 1993 Scientific Assembly of Radiological Society of North America. Address reprint requests to S. Vijayakumar, Michael Reese Hospital and Medical Center, Dept. of Radiation Oncology, Room 149 MR, 2929 S Ellis Ave, Chicago, IL 60616.

TABLE 1. PATIENT CHARACTERISTICS

	No. Patients (%)		
	Group 1	Group 2	Groups 1 & 2
Median age (years)	67	72	70
Total no.	19	17	36
Race			
African American	14 (73.7)	7 (41.2)	21 (58.3)
White	5 (26.3)	10 (58.8)	15 (41.7)
Stage			
A	a (5.3)	3 (17.6)	4 (11.1)
B	12 (63.2)	13 (76.5)	25 (69.4)
C	6 (31.6)	1 (5.9)	7 (19.4)
Grade			
1	0 (0.0)	2 (11.8)	2 (5.6)
2	11 (57.9)	9 (52.9)	20 (55.6)
3	8 (42.1)	6 (35.3)	14 (38.9)

biopsy, and the volume of the prostate gland. The influence of these factors on serum PSA levels has been well studied. However, whether serum male hormone levels can influence serum PSA levels has not been studied. Because both prostate glandular cells and prostate cancer cells are male hormone-dependent, such an influence is possible. This article reports the results of a cross-sectional study addressing this issue.

MATERIALS AND METHODS

Clinical Protocol

Blood samples were collected prospectively in 19 patients (group 1) who had had no hormone treatment and were referred to the radiation oncology department for treatment for localized (clinical stages A-C) prostate cancer. All patients had a bone scan, a chest roentgenogram, and computerized tomography of the pelvis to exclude any metastatic disease. Blood samples were collected prior to digital rectal examination or radiotherapy. Three blood samples were collected 10 minutes apart between 9:00 AM and 9:30 AM for each patient and pooled together to avoid diurnal and episodic variation in serum testosterone values.[2,3]

Only one blood sample was collected prior to any treatment and not always between 9:00 AM and 9:30 AM from another group (group 2) of 17 similarly staged patients who also were referred for radiation therapy with stage A-C prostate cancer. This group represents patients whose serum samples were collected as part of another study prior to the initiation of the protocol for group 1 as described above.

Serum Hormone Determination

Serum levels of PSA and four hormones—androstenedione, free testosterone, luteinizing hormone, and prolactin—were determined for all patients.

Androstenedione Determination. Levels of androstenedione were determined by using a solid-phase radioimmunoassay reagent from Diagnostic System Laboratories Inc. In this procedure, androstenedione in the 50 μL-serum competes with the ^{125}I-radiolabeled androstenedione (500 μL) to bind on the antibody that is coated on the tube during 40 minutes of incubation at 37°C. The unbound radiolabeled antigen (^{125}I androstenedione) then is removed by decanting the tubes. The amount of ^{125}I-labeled androstenedione bound to the antibody is inversely proportional to the concentration of androstenedione present in the serum, which is read against a standard curve. The normal range for androstenedione is 0.30 to 3.10 ng/mL.

Free Testosterone Determination. Free testosterone was measured in the patient's serum using Diagnostic Products Corporation's solid phase radioimmunoassay reagents. In this procedure, the ^{125}I labeled testosterone analog competes with free testosterone of the patient's sample (50 μL) for the sites on testosterone-specific antibody coated on the inside wall of a polypropylene tube. Then the bound and free tracer fraction is separated by decanting the tube and counted on a gamma counter. The counts are inversely related to the concentration of free testosterone that is determined by using a standard curve. Free testosterone normal serum levels in men range from 10 to 40 pg/mL.

Luteinizing Hormone Determination. The analysis of luteinizing hormone was performed by using Diagnostic Products Corporation's Coated Immunoradiometric Assay. Two hundred μL of the patient's sample is incubated with a fixed amount of ^{125}I-labeled antibody in an luteinizing hormone antibody-coated tube for 1 hour at room temperature. Luteinizing hormone present in the sample is sandwiched between the tracer and solid-phase (coated tube) antibodies. The unbound tracer is decanted, and the remainder is counted on a gamma counter for 1 minute. The concentration of luteinizing hormone is directly proportional to the counts, which is determined by comparing against a standard curve. Suggested normal range for luteinizing hormone in men is 2 to 12 IU/mL.

Prolactin Determination. The prolactin levels in the patient's sera were determined using Diagnostic Products Corporation's coat-a-count (solid phase) radioimmunoassay. Two hundred μL of the patients' sample is incubated with 1 μL of ^{125}I-labeled prolactin tracer in an antiprolactin antibody-coated tube for 18 hours at room temperature. At the end of the incubation, the unbound tracer is decanted. The tubes then are counted in a gamma counter. The count of the tube is inversely proportional to the con-

TABLE 2. SERUM PROSTATE SPECIFIC ANTIGEN AND HORMONAL VALUES

	PSA (ng/mL)	LH (IU/mL)	PRL (ng/mL)	ASD (ng/mL)	FT (pg/mL)
Group 1*					
Range	0.5-80.1	0.5-4.7	1.2-33.3	0.3-2.5	6.2-17.1
Median	11.8	1.4	6.8	1.3	11.8
Mean	23.7	1.7	8.8	1.2	12.4
Group 2†					
Range	1.4-61.1	0.8-5.8	0.0-29.5	0.7-2.7	7.8-41.3
Median	17.6	1.9	5.9	1.7	13.4
Mean	20.6	2.1	7.9	1.7	15.2
Groups 1 & 2 Combined‡					
Range	0.5-80.1	0.5-5.8	0.0-33.3	0.3-2.7	6.2-41.3
Median	13.1	1.6	6.0	1.4	13.3
Mean	22.2	1.9	8.4	1.4	13.7

Abbreviations: PSA=prostate specific antigen, LH=leutinizing hormone, PRL=prolactin, ASD=androstenedione, and FT=free testosterone.
*n=19.
†n=17.
‡N=36.

centration of prolactin, which is determined by comparing the counts against a standard curve of known concentration. Diagnostic Products Corporation's recommended range for prolactin in men is 0 to 15 ng/mL.

Prostate Specific Antigen Determination. The PSA concentration in each patient's serum was determined using Hybritech's Tandem-R PSA assay, which is based on a solid-phase two-site immunoradiometric technique. Serum samples (50 μL) containing PSA are allowed to react with an immobilized monoclonal antibody coated on plastic beads (solid phase) and simultaneously with a fixed amount (200 μL) of ^{125}I-labeled monoclonal antibody. These two antibodies are directed against two different but unique epitopes of the PSA molecule. Following a sandwich formation (solid-phase antibody/PSA antigen/^{125}I labeled antibody), the bead is washed twice to remove the excess unbound radioactive labeled antibody. The radioactivity bound to the antigen is measured on a gamma counter. The counts are directly proportional to the concentration of PSA, which is determined by referring to a standard curve. Normal PSA concentration range in our laboratory is 0 to 4 ng/mL.

Statistical Methods

The influence of androstenedione, free testosterone, prolactin, and luteinizing hormone on PSA levels were examined using simple regression. Age, race, stage of cancer, and grade of tumor also were included in a subsequent multivariate analysis of each hormone. Analyses were carried out separately for groups 1 and 2, as well as after combining the data. The logarithm of PSA was taken to remove the skewness of the distribution of PSA values in regression analysis. Comparison of hormonal values between African Americans and whites were performed using two sample *t*-tests; again, a log transformation was introduced. Such comparisons were made since previous reports show racial differences in testosterone levels (vide infra).

RESULTS

Table 1 details patient characteristics and tumor stage and grade. Table 2 lists range, median, and mean values for PSA and hormonal levels. In group 1, patients' ages ranged from 56 to 81 years (mean: 67.8 years). Prostate specific antigen values ranged from 0.5 to 80.1 ng/mL (mean: 23.7 ng/mL). Fourteen of 19 patients in group 1 were African Americans. In group 2, patients' ages ranged from 58 to 85 (mean: 71.9 years); mean PSA was 20.6 ng/mL (range: 1.4 to 61.1 ng/mL). Seven patients in group 2 were African Americans. Overall, for groups 1 and 2 combined, patients ages ranged from 56 to 85 (mean: 69.8 years). Four patients were stage A2, 25 were stage B, and 7 were stage C patients. The breakdown for grades 1, 2, and 3 were 2, 20, and 14 patients, respectively.

Table 3 shows the influence each hormone alone has on the PSA level. None were significant within group 1 or group 2. However, the patients in group 1 averaged significantly lower serum androstenedione levels than those in group 2. None of the other mean hormonal levels significantly differed between groups 1 and 2. For pooled data, prolactin seems to be significantly associated with

TABLE 2. RESULTS OF UNIVARIATE ANALYSIS*

	Intercept	Slope	SD	*t*-Test Statistic	*P* Value
Group 1					
Androstenedione	3.01	−0.40	0.46	−0.87	−.395
Testosterone	1.90	0.05	0.11	0.47	.645
Prolactin	3.10	−0.066	0.039	−1.68	.112
Luteinizing hormone	2.74	−0.12	0.28	−0.43	.673
Age	3.78	−0.018	0.045	−0.41	.688
Group 2					
Androstenedione	2.12	0.24	0.49	0.49	.628
Testosterone	1.66	0.060	0.037	1.55	.142
Prolactin	3.13	−0.075	0.041	−1.85	.084†
Luteinizing hormone	2.47	−0.028	0.26	0.11	.915
Age	2.91	−0.0051	0.049	−0.11	.917
Androstenedione	2.69	−0.11	0.31	−0.37	.717
Testosterone	1.80	0.053	0.036	1.47	.150
Prolactin	3.11	−0.069	0.027	−2.53	.016†
Luteinzing hormone	2.62	−0.047	0.18	−0.25	.801
Age	3.35	−0.012	0.031	−0.38	0.704

COMPARISON BETWEEN GROUPS 1 AND 2

	Mean Difference (Group1-Group2)	*t*-Test	*P* Value
Androstenedione	−0.51	−2.38	.023
Testosterone	−2.82	−1.47	.156
Prolactin	0.94	0.40	.694
Luteinizing hormone	−0.43	−1.12	.269

Abbreviations: SD=standard deviation.
*Model: log(PSA)=a+bx.
†Statistically significant or marginally significant.

PSA level (P=.016); note that for group 2, the P value is .084. The serum PSA levels exponentially declined with an increase in prolactin levels. On multivariate analysis, no hormone had significant effect on PSA or on each other's concentration after each being adjusted for known influential factors such as stage, grade, race, and age either within both group or for pooled data.

The data in Table 4 show no racial differences in hormone levels except for luteinizing hormone. The mean log luteinizing hormone values were lower in African Americans than in whites for group 2 (P=.022) and for pooled data (P=.005).

DISCUSSION

Prostate cancer is a male hormone-dependant cancer. Prostate cancer develops in rats after prolonged administration of testosterone. However, prostate cancer never develops in men castrated before puberty. The incidence of prostate cancer is low in patients with cirrhosis and resultant hyperestrogenism. High androgen receptor levels are seen in cancerous prostatic tissues. Finally, prostate cancer (either metastatic or nonmetastatic) responds to surgical or medical ablation of male hormones.[4-8]

This study was designed to determine whether serum male hormone levels influence serum PSA levels if different patients have similar tumor cell burdens and tumors with similar pathological differentiation and whether such an influence is responsible for the overlap in PSA levels between patients with different stages and grades of prostate cancers. Patients with metastatic disease were excluded because such patients can have highly variable tumor cell burdens, eg, a single area of positive bone scan versus a "super scan." Patients with organ-confined prostate cancer are likely to have a narrower range of tumor cell burden.

No correlation was found between serum PSA levels and serum concentrations of androstenedione, free testosterone, or luteinizing hormone in our analyses. Although serum prolactin levels were associated with PSA concentration, that association disappeared on the multivariate analysis after adjusting for stage and grade of tumor, and age and race of patient. The measurement of prolactin was

TABLE 3. RACIAL COMPARISON

Serum Levels	Mean	SD	SE	Min	Max	*P* Value
Group 1						
Androstenedione						
African American	1.136	0.681	0.182	0.3	2.5	.537
White	1.360	0.691	0.309	0.5	2.3	
Testosterone						
African American	11.986	2.782	0.744	6.2	17.1	.374
White	13.380	3.369	1.506	8.8	17.1	
Prolactin						
African American	7.200	4.239	1.133	1.8	17.6	.341
White	13.400	12.695	5.677	1.2	33.3	
Luteinizing hormone						
African American	1.379	0.674	0.180	0.5	2.6	.170
White	2.620	1.645	0.736	1.2	4.7	
Group 2						
Androstenedione						
African American	2.000	0.606	0.229	0.8	2.6	.096
White	1.500	0.547	0.173	0.7	2.7	
Testosterone						
African American	14.414	3.926	1.484	10.0	22.0	.701
White	15.710	9.302	2.942	7.8	41.3	
Prolactin						
African American	9.871	8.859	3.348	4.5	29.5	.318
White	6.500	4.544	1.437	0.0	15.1	
Luteinizing hormone						
African American	1.457	0.424	0.160	0.8	2.0	.022*
White	2.600	1.275	0.403	1.2	5.8	
Pooled (Groups 1 & 2 Combined)						
Androstenedione						
African American	1.424	0.765	0.167	0.3	2.6	.901
White	1.453	0.578	0.149	0.5	2.7	
Testosterone						
African American	12.795	3.322	0.725	6.2	22.0	.329
White	14.933	7.757	2.003	7.8	41.3	
Prolactin						
African American	8.090	6.074	1.325	1.8	29.5	.770
White	8.800	8.406	2.170	0.0	33.3	
Luteinizing hormone						
African American	1.405	0.592	0.129	0.5	2.6	.005*
White	2.607	1.349	0.348	1.2	5.8	

Abbreviations: SD=standard deviation, SE standard error, Min=minimum, and Max=maximum.
*n=14 African Americans and 5 whites.
†n=7 African Americans and 10 whites.
‡Statistically significant.
§N=21 African Americans and 15 whites.

performed since several reports cite its influence on prostate physiology.[9-13] High prolactin levels are seen in some prostate cancer patients.[14,15] In two other studies, prolactin levels were reported to be comparatively higher in patients with BPH than in the controls and also relatively higher in patients with prostate cancer than in those with BPH.[15,16] In view of this, a significant correlation found between prolactin levels and PSA levels in the univariate analysis for the pooled data is of interest. However, we are unable to explain or assign any importance to our finding at this time. Given the influence of prolactin on prostate tissue, further studies are needed. The lack of any racial difference in the testosterone and androstenedione levels in our population is an important

finding. We analyzed for any racial differences because of previous reports in young college students showing such differences.[17,18] Previously, Ross et al[17] found the serum total and free testosterone levels in young (age range: 18 to 22 years) African-American men to be about 15% higher than in white men (P=.02); the estrone levels were also higher (P=.05). Ross et al hypothesized that the higher serum testosterone levels were responsible for a higher incidence of prostate cancer in African Americans. More recently, the same group[18] compared the serum testosterone, sex hormone binding globulin, 3-α, 17-β androstanediol glucuronide, and androsterone glucuronide between young US and Japanese college students. Young US African Americans had about 11% higher (640 ng/mL) mean testosterone levels than whites (575 ng/mL) while young Japanese men had intermediate levels (602 ng/mL). The 17-β androstanediol glucuronide (P<.01), androsterone glucuronide (P<.05), and sex hormone binding globulin (P<.01) levels were lower in young Japanese men than in the US cohort.

In our study population of prostate cancer patients, with a mean age of 70 years, no differences were found between whites and African-Americans in testosterone, androstenedione, or prolactin levels. The lack of any difference in the testosterone levels in our study in contrast to the younger population in the study by Ross et al[18] is interesting. It is possible that any difference in testosterone levels between US African Americans and whites at a younger age group may disappear with aging; it is also possible that such racial differences may be confined to one geographic region. In addition, all of our patients harbored prostate cancer whereas Ross et al studied normal men.

However, we found a racial difference in mean serum luteinizing hormone levels, the values being higher in whites than in African Americans. Luteinizing hormone secretion is inhibited by release of testosterone (and estrogen) in the circulation.[19] Luteinizing hormone levels in men are influenced by both testosterone and estrogen levels.[19] About 75% to 90% of circulating estrogens in men result from peripheral conversion of androstenedione and testosterone to estrone and estradiol, respectively.[19] After the age of 50, estradiol levels in men have been noted to increase approximately 50%, with an increase in free estradiol to free testosterone ratio by approximately 40%.[19] Such changes in the ratio can in turn reduce luteinizing hormone release. It is well known that diet also can influence serum hormonal levels significantly.[20,21] We can only speculate that such causes may be responsible for the racial differences in luteinizing hormone levels in our population.

Our results suggest that differences in levels of the four hormones studied are unlikely to cause an effect on PSA concentration among patients with similar stage and grade prostate cancer. However, our study suffers from the following shortcomings: the sample size may be too small to detect any minor influence; we did not determine dihydrotestosterone levels. Testosterone is converted to dihydrotestosterone in the prostate gland with 5-alpha reductase enzyme acting as a catalyst.[18,22,23] Inhibition of 5-alpha reductase reduces progression of prostate cancer.[24,25] Metabolites in serum, which reflect 5-alpha reductase activity and in turn the intraprostatic dihydrotestosterone levels such as 17-β androstanediol glucuronide and androsterone glucuronide, are higher in American males (who are at greater risk of developing prostate cancer) than in Japanese men, although no differences in testosterone levels were found.[18] For these reasons, intraprostatic and serum dihydrotestosterone levels may influence PSA concentrations. Further studies are needed.

CONCLUSION

Serum hormones determined in this study (free testosterone, androstenedione, luteinizing hormone, and prolactin) do not appear to influence PSA levels in prostate cancer patients, although prolactin levels were associated with PSA levels in the univariate analysis; whether dihydrotestosterone levels or estrogen levels may have such an influence was not studied. No difference in serum hormonal levels was found between African Americans and whites in this age group, except for luteinizing hormone, which was lower in African-American prostate cancer patients; the importance of this is not known. Only a comprehensive study involving a large number of patients in which serum levels of a panel of hormones (luteinizing hormone, follicular stimulating hormone, testosterone, androstenedione, 17-β androstanediol glucuronide, androsterone glucuronide, estrone, E_2, prolactin, and dihydrotestosterone) can answer many questions raised by this study and others.[5,14,19] A large-scale prevention trial involving 18,000 men over the age of 55 and without prostate cancer is being conducted in which serum samples are being collected; this provides a unique opportunity to study the influence of various hormones on prostatic physiology.

Acknowledgments

The authors thank Ms Evelyn Davison for her secretarial assistance and Alan Jackson, MD, for reviewing the manuscript.

Literature Cited

1. Gerber GS. Prostate specific antigen. *Principles & Practice of Oncology Updates.* 1993;7.
2. De Lacerda L, Kowarski A, Johanson AJ, Athanaiou R,

Migeon CJ. Integrated concentration and circadian variation of plasma testosterone in normal men. *J Clin Endocrinol Metab.* 1973;37:366-371.

3. Goldzieher JW, Dozier TS, Smith D, Steinberger E. Improving the diagnostic reliability of rapidly fluctuating plasma hormone levels by optimized multiple sampling techniques. *J Clin Endocrinol Metab.* 1976;43:824-830.

4. Glantz GM. Cirrhosis and carcinoma of the prostate gland. *J Urol.* 1964;91:291-293.

5. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. *Cancer Res.* 1982;42:3232-3239.

6. Hovenian MS, Deming CL. The heterologous growth of cancer of the human prostate. *Surg Gynecol Obstet.* 1948;86:29-35.

7. Huggins C, Hodges CV. Studies on prostatic cancer: effect of castration, of estrogen, and of androgen injection on serum phosphastases in metastatic carcinoma of the prostate. *Cancer Res.* 1941;1:293-297.

8. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res.* 1977;37:1929-1933.

9. Chase MD, Geschwind II, Bern HA. Synergistic role of prolactin in response of male rat sex accessories to androgen. *Proc. Soc. Exp. Biol. Med.* 1957;94:680-683.

10. Grayhack JT, Lebowitz JM. Effect of prolactin on citric acid of lateral lobe of prostate of Sprague-Dawley rat. *Investve Urol.* 1967;5:87-94.

11. Hafiez AA, Lloyd CW, Bartke A. The role of prolactin in the regulation of testis function: the effects of prolactin and luteinizing hormone on the plasma levels of testosterone and androstenedione in hypophysectomized rats. *J Endocrinol.* 1972;52:327-332.

12. Johansson R. Effect of prolactin, growth hormone and insulin on the uptake and binding of dihydrotestosterone to the cultured rat ventral prostate. *Acta Endocr Copenh*. 1976;81:854-864.

13. Farnsworth WE, Gonder MJ. Prolactin and prostate cancer. *Urology.* 1977;10:33-34.

14. Wynder EL, Laakso K, Sotarauta M, Rose DP. Metabolic epidemiology of prostatic cancer. *Prostate.* 1984;5:47-53.

15. Saroff J, Kirdani RY, Chu TM, Wajsman Z, Murphy GP. Measurements of prolactin and androgens in patients with prostatic diseases. *Oncology.* 1980;37:46-52.

16. Harper ME, Peeling WB, Cowley T, Brownsey BG, Phillips MEA, Groom G, etal. Plasma steroid and protein hormone concentrations in patients with prostatic carcinoma, before and during oestrogen therapy. *Acta Endocr Copenh*. 1976;81:409-426.

17. Ross R, Bernstein L, Judd H, Hanisch R, Pike M, Henderson B. Serum testosterone levels in healthy young black and white men. *J Natl Cancer Inst.* 1986;76:45-48.

18. Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, et al. Evidence for reduced 5-alpha-reductase activity in Japanese compared to US Caucasian and African-American males: implications for prostate cancer risk. *Lancet.* 1992;339:887.

19. Sandberg AA: Endocrine control and physiology of the prostate. *Prostate.* 1980;1:169-184.

20. Hill PB, Wynder EL. Effect of a vegetarian diet and dexamethasone on plasma prolactin, testosterone and dehydroepiandrosterone in men and women. *Cancer Lett*. 1979;7:273-282.

21. Hill P, Wynder EL, Garbaczewski L, Garnes H, Walker ARP. Diet and urinary steroids in black and white North American men and black South African men. *Cancer Res*. 1979;39:5101-5105.

22. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5-alpha reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science.* 1974;186:1213-1215.

23. Walsh PC, Madden JD, Harrod MJ, Goldstein JL; MacDonald PC, Wilson JD. Familial incomplete male pseudohermaphroditism, type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *N Engl J Med*. 1974;291:944-949.

24. Kadohama N, Karr JP, Murphy GP, Sandberg AA. Selective inhibition of prostatic tumor 5-alpha reductase by a 5-methyl-4-aza-steroid. *Cancer Res.* 1984;44:947-954.

25. Petrow V, Padilla GM, Mukherji S, Marts SA. Endocrine dependence of prostatic cancer upon dihydrotestosterone and not upon testosterone. *J Pharm Pharmacol.* 1984;36:352.